Review

Dietary fat intake and ovarian cancer risk: a meta-analysis of epidemiological studies

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ABSTRACT

Observational studies assessing the association of dietary fat and risk of ovarian cancer yield discrepant results. Pertinent prospective cohort studies were identified by a PubMed search from inception to December 2015. Sixteen independent case-control and nine cohort studies on dietary fat intake were included, with approximately 900,000 subjects in total. Relative risks (RRs) with 95% confidence intervals were pooled using a random effects model. Heterogeneity, sensitivity analysis and publication bias were assessed; subgroup analysis and analysis stratified by EOC histology were conducted. The reported studies showed a significant increase of ovarian cancer risk with high consumption of total-, saturated-, and trans-fats, while serous ovarian cancer was more susceptible to dietary fat consumption than other pathological subtypes. No evidence of positive association between dietary fat intake and ovarian cancer risk was provided by cohort studies. Menopausal status, hormone replacement therapy, body mass index (BMI), and pregnancy times, modified the objective associations. In conclusion, the meta-analysis findings indicate that high consumption of total, saturated and trans-fats increase ovarian cancer risk, and different histological subtypes have different susceptibility to dietary fat.

INTRODUCTION

Ovarian cancer is considered the sixth most commonly diagnosed cancer among women and the second cause of gynecologic cancer mortality worldwide [1, 2]. The prognosis of ovarian cancer is poor, with the initial diagnosis in most patients made at an advanced stage [3, 4]. The noticeable relationship between ovarian cancer incidence and geographical regions suggested that dietary habits and ethnic variations are potentially modifiable factors [5], whose etiologic role in ovarian cancer risk, however, remains undefined [6].

Dietary fat, as one of the most controversial dietary factors in nutritional epidemiology, has been reported with positive correlations with breast [7] and gastric [8] cancers in two recent meta-analyses, and elevated ovarian cancer risk in early ecologic studies [5, 9]. Although multiple epidemiologic studies have explored the associations between dietary fat consumption and risk of ovarian cancer, no definite conclusion have been drawn, and the dietary fat varieties as well as pathological types of ovarian cancer increase the complexity of this research topic. The results of two meta-analyses [10, 11] and a pooled analysis [12] that included data from 12 cohort studies also reached inconsistent conclusions. Therefore, we conducted a meta-analysis of case-control and cohort studies with more-detailed analyses of 1) the epidemiologic evidence regarding the association of dietary fat consumption with risk of ovarian cancer, 2) the association between dietary fat intake and the risk of ovarian cancer and pathological subtypes. This analysis was based on dietary fat types, and we extended the previous analyses [10, 11] with more included studies and dietary fat types, and an assessment stratified by EOC histology.

RESULTS

We found 1421 publications from the electronic and manual literature searches. Thirty-three potentially relevant publications [16-31] [32-47] [48] appeared to

meet the specified protocol inclusion criteria after initial screening. Through further reading, six publications [41-46] contained no relevant dietary fat; two publications [47, 48] were excluded for design and dietary fat classification. Two American publications [17, 18] assessed the same study population, and eligible data were extracted from both; two Chinese publications were treated likewise [25, 28] (Figure 1).

Finally, Twenty-five publications [16-31] [32-40], including sixteen case-control [16-31] (Table 1) and nine cohort [32-40] (Table 2) studies were included in the analysis of dietary fat intake and ovarian cancer risk. Results were separated by dietary fat types, including total, saturated, monounsaturated, polyunsaturated, animal, plant, dairy fat, and trans-fats.

Total fat

Eleven case-control and six cohort studies assessed total fat intake and ovarian cancer risk. Summary RR was 1.32 (95% CI = 1.06-1.63, $P = 0.017$) for case-control and 1.10 (95% CI = 0.97-1.24, $P = 0.25$) for cohort studies, with an overall RR of 1.19 (95% CI = 1.04-1.37, $P = 0.015$) for all studies. These results suggested a positive association between total fat intake and ovarian cancer risk. (Figure 2)

Animal fat

Five case-control and five cohort studies analyzed animal fat intake and ovarian cancer risk. Summary RR was 1.50 (95% CI = 0.89-2.53, $P = 0.125$) for case-control, and 1.09 (95% CI = 0.93-1.28, $P = 0.272$) for cohort studies; the overall RR was 1.21 (95% CI = 0.99-1.47, $P = 0.065$) for all studies. Taken together, these results suggested no association between animal fat intake and ovarian cancer risk. (Figure 3)

Plant fat

Four case-control and five cohort studies evaluated plant fat intake and ovarian cancer risk. Summary RR was 0.96 (95% CI = 0.81-1.12, $P = 0.586$) for case-control, and 0.93 (95% CI = 0.74-1.17, $P = 0.053$) for cohort studies, with an overall RR of 0.95 (95% CI = 0.83-1.09, $P = 0.472$). These results suggested no association between plant fat intake and ovarian cancer risk. (Figure 4)

Saturated fat

Seven case-control and six cohort studies assessed saturated fat intake and ovarian risk. Summary RR was 1.11 (95% CI = 0.98-1.27, $P = 0.147$) for case-control, and 1.06 (95% CI = 0.89-1.26, $P = 0.0.521$) for cohort studies; the overall RR was 1.09 (95% CI = 0.98-1.21, $P = 0.103$). After exclusion of 1 study [29] for small bias and sensitivity data, the results changed as follows, respectively, 1.15 (95% CI = 1.02-1.30, $P = 0.026$), 1.06 (95% CI = 0.89-1.26, $P = 0.521$), 1.12 (95%CI = 1.02-1.22, $P = 0.014$), without heterogeneity ($Q = 8.54$, $P = 0.577$, $I2 = 0.0\%$) between studies. These results suggested a positive association between saturated fat intake and ovarian cancer risk. (Figure 5)

Monounsaturated fat

Eight case-control and five cohort studies analyzed monounsaturated fat intake and ovarian cancer risk. Summary RR was 0.96 (95% CI = 0.83-1.12, $P = 0.477$) for case-control, and 1.04 (95% CI = 0.88-1.22, $P = 0.649$) for cohort studies; the overall RR was 0.98 (95% CI = 0.87-1.09, $P = 0.556$) for all studies. These results suggested no association between total fat intake and ovarian cancer risk. (Figure 6)

Polyunsaturated fat

Eight case-control and five cohort studies involved polyunsaturated fat intake and ovarian cancer risk. Summary RR was 0.92 (95% CI = 0.81-1.04, $P = 0.223$) for case-control, and 1.06 (95% CI = 0.86-1.31, $P = 0.570$) for cohort studies, with an overall RR of 0.97 (95% CI = 0.86-1.10, $P = 0.760$) for all studies. These findings suggested no association between polyunsaturated fat intake and ovarian cancer risk. (Figure 7)

Dairy fat

One case-control and five cohort studies assessed dairy fat intake and the risk of ovarian cancer. Summary RR was 1.10 (95% CI = 0.94-1.28, $P = 0.242$) for cohort studies, with an overall RR of 1.05 (95% CI = 0.92-1.19, $P = 0.478$) for all studies. These results suggested no association between dairy fat intake and ovarian cancer risk. (Figure 8)

Trans-fat

Two case-control and two cohort studies evaluated trans-fat intake and ovarian cancer risk. Summary RR was 1.25 (95%CI = 1.06-1.49, $P = 0.010$) for case-control, and 1.24 (95% CI = 0.85-1.81, $P = 0.285$) for cohort studies; the overall RR was 1.25 (95% CI = 1.08-1.44, $P = 0.002$) for all studies. These results suggested a significant positive association between trans-fat intake and ovarian cancer risk. (Figure 9)

Table 1:The characteristics and relative risks [RRs; 95% confidence interval (CI)] for case-control studies on dietary fat and ovarian cancer

Author (Country)	Publication yr	Case/Control	Type of Fat	RR (95% CI)	Adjusted confounding factors
Cramer[16] (America)	1984 (1978-1981)	215/215	Animal fat	1.83 (1.00-3.38)	Weight/height^2
Risch[17, 18] (Canada)	1994 (1989-1992)	450/564	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	1.16 (0.86-1.57) 1.23 (0.97-1.58) 1.07 (0.90-1.27) 0.86 (0.69-1.07)	Age, total calorie intake, no. of full-term pregnancies, duration of OC use
Shu[19] (China)	1989 (1984-1986)	172/172	Total fat Animal fat Plant fat	1.9 (1.2-4.4) 1.7 (1.0-3.2) 0.8 (0.4-1.4)	income, no. of live births, history of ovarian cysts, smoking history, OC use, IUD use, tubal ligation
Slattery[20] (America)	1989 (1984-1987)	85/492	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	1.3 (0.7-2.3) 1.3 (0.6-2.6) 1.3 (0.7-2.3) 1.2 (0.6-2.3)	Age, BMI, no. of pregnancies
Tzonou[21] (Greece)	1993 (1989-1991)	189/200	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	0.97 (0.76-1.24) 1.17 (0.88-1.55) 0.86 (0.71-1.05) 0.95 (0.77-1.17)	Age, years of schooling, parity, age at 1st birth, menopausal status, energy intake
La Vecchia[22] (Italy)	1987 (1983-1986)	455/1385	Total fat	2.14 (1.59-2.88)	Age, interviewer, marital status, social class, education, parity, age at 1st birth, age at menarche, menopausal
Webb[23] (Australia)	1998 (1990-1993)	824/1132	Total fat	1.86 (1.03-3.37)	Age, education, BMI, smoking, parity, OC use, total energy intake
Pan[24] (Canada)	2004 (1994-1997)	442/2135	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat	1.21 (0.88 -1.65) 1.06 (0.78- 1.45) 1.26 (0.92-1.72) 1.28 (0.94 -1.76)	Age, residence, education, alcohol consumption, smoking, BMI, caloric intake, recreational physical activity, number of live births, menstruation years, and menopause status
Zhang[25] (China)	2002 (1999-2000)	254/652	Animal fat Plant fat	4.55 (2.2-9.3) 1.03 (0.6-1.9)	Age, residence, education, alcohol consumption, smoking, BMI, tube ligation, menopause status
McCann[26] (America)	2003 (1986-1991)	124/696	Total fat Saturated fatty acid Monounsaturated fat Polyunsaturated fat	1.51 (0.57–4.02) 1.46 (0.68–3.15) 1.77 (0.73–4.31) 0.63 (0.28–1.41)	Age, education, total months menstruating, difficulty becoming pregnant, OC use, menopausal status and total energy intake
Merritt[27] (America)	2014 (1992-2008)	1872/1978	Total fat Animal fat Dairy fat Saturated fat Plant fat Trans fat Monounsaturated fat Polyunsaturated fat	1.07 (0.89-1.29) 1.04 (0.87-1.26) 0.95 (0.79-1.14) 1.11 (0.92-1.34) 0.98 (0.81-1.17) 1.30 (1.08-1.57) 0.97 (0.81-1.18) 0.82 (0.68-0.99)	Age, study centre (MA, NH), study phase, number of pregnancies, OC use, family history of ovarian cancer tubal ligation

Zhang[28] (China)	2003 (1999-2000)	254/652	Total fat	2.17 (1.26-3.75)	Age, locality, education, family income, BMI, total energy intake, tobacco smoking, alcohol ,parity, menopausal status, OC use
Salazar-Martinez[29] (Mexico)	2002 (1995-1997)	84/629	Total fat Saturated fat Monounsaturated fat Polyunsaturated fat Animal fat Plant fat	0.60 (0.33-1.06) 0.56 (0.31-1.02) 0.54 (0.30-0.99) 0.61 (0.34-1.11) 0.66 (0.37-1.19) 0.81 (0.46-1.45)	Age, weight change, total energy intake, number of live births, physical activity, diabetes
Chiaffarino[30] (Italy)	2007 (1992-1999)	750/2411	Monounsaturated fat Polyunsaturated fat	0.80 (0.66-0.96) 0.96 (0.76-1.21)	education, parity, oral contraceptive use, family history of ovarian and/ or breast cancer in first degree relatives
Hu[31] (Canada)	2011 (1994-1997)	442/5039	Trans fat	1.04 (0.68-1.58)	Age, province, education, BMI, alcohol drinking, pack-year smoking, total of vegetable and fruit intake, monounsaturated fat, polyunsaturated fat, total energy intake, number of live births and years of menstruation

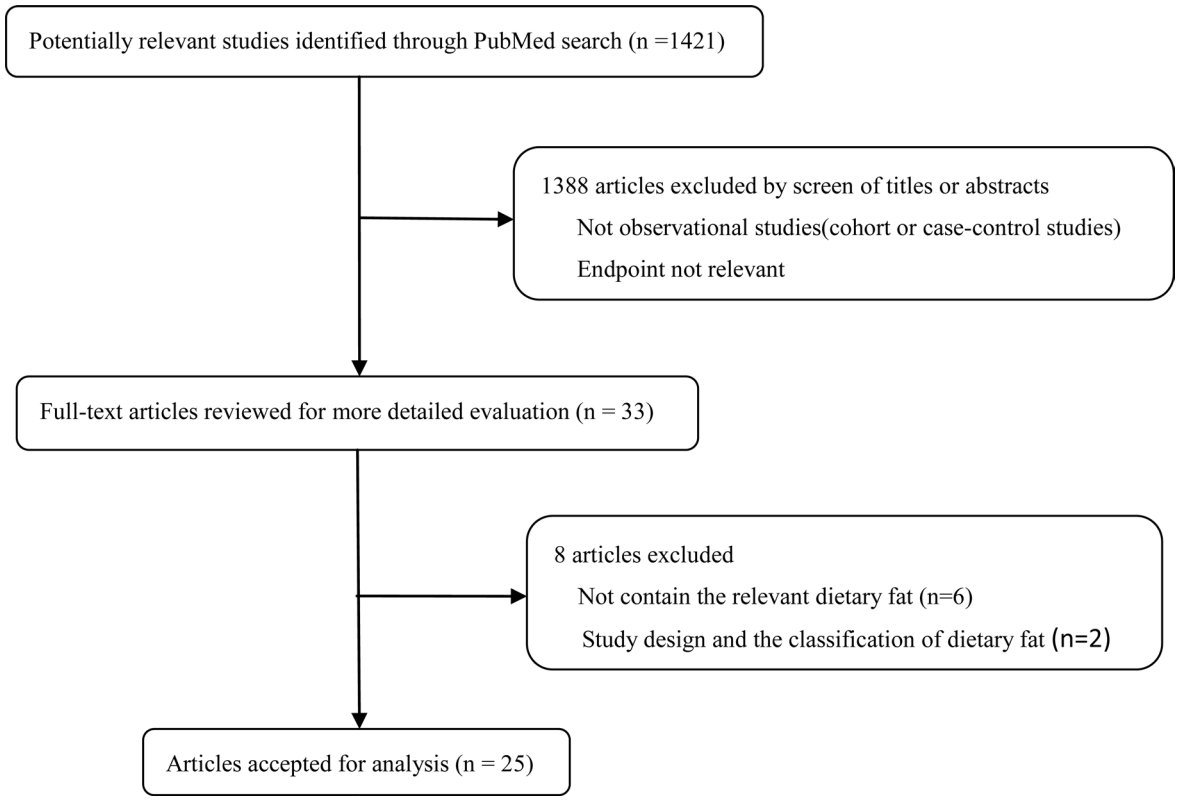

Figure 1: Flow chart.

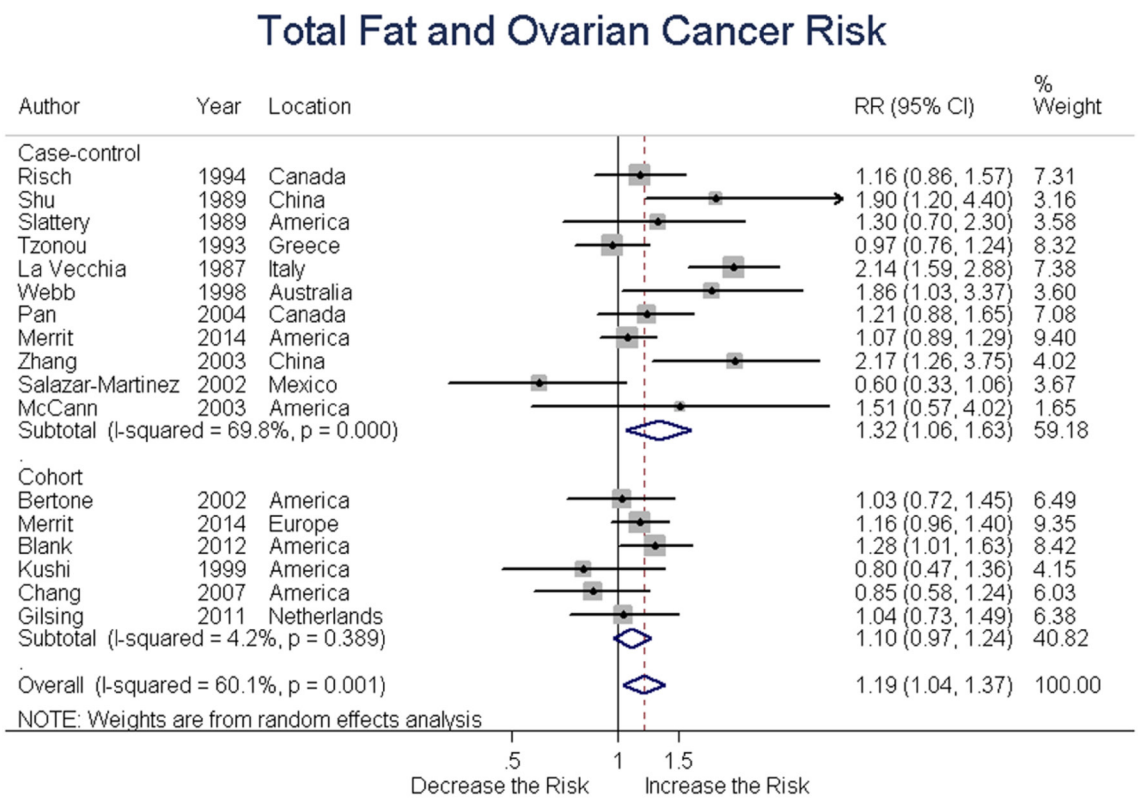

Figure 2: Relationship between total fat intake and ovarian cancer risk.

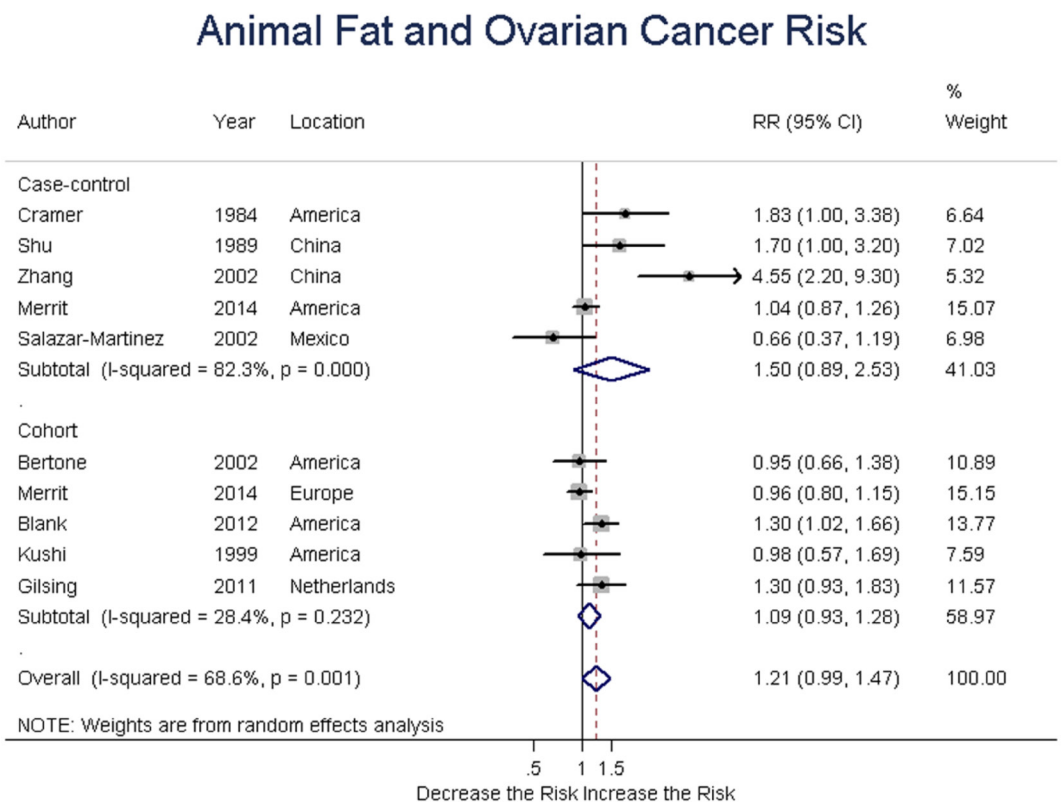

Figure 3: Relationship between animal fat intake and ovarian cancer risk.

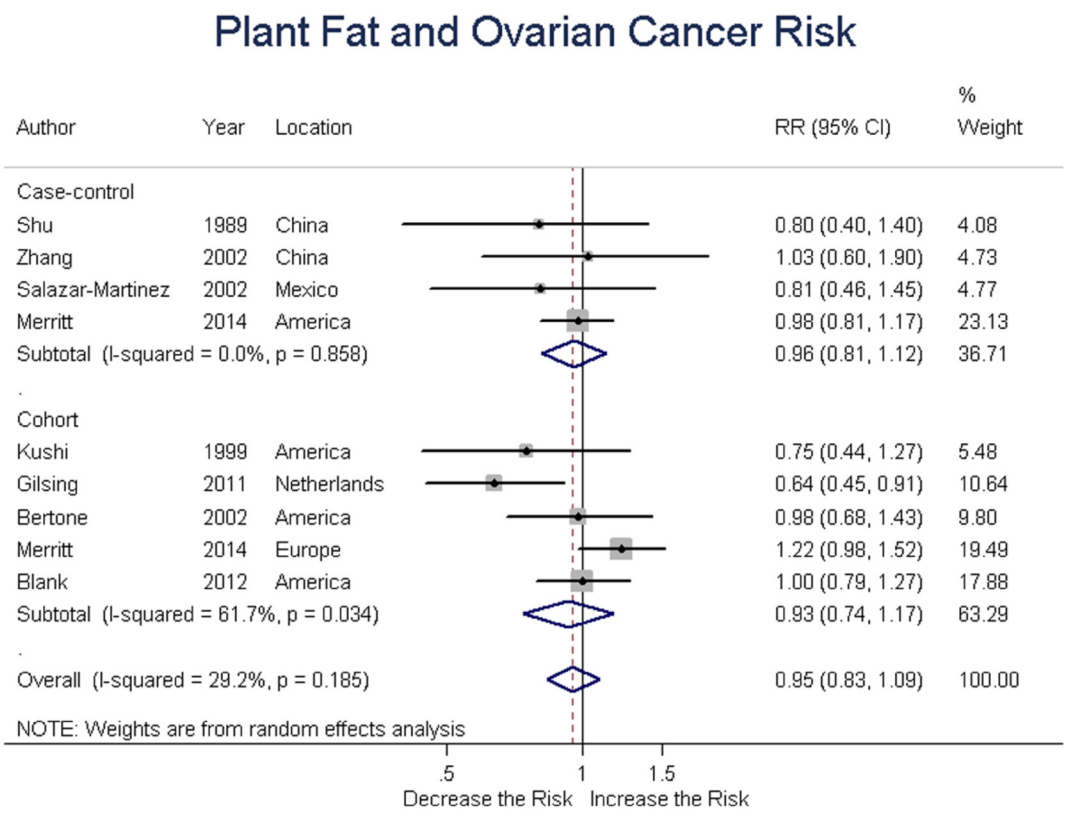

Figure 4: Relationship between plant fat intake and ovarian cancer risk.

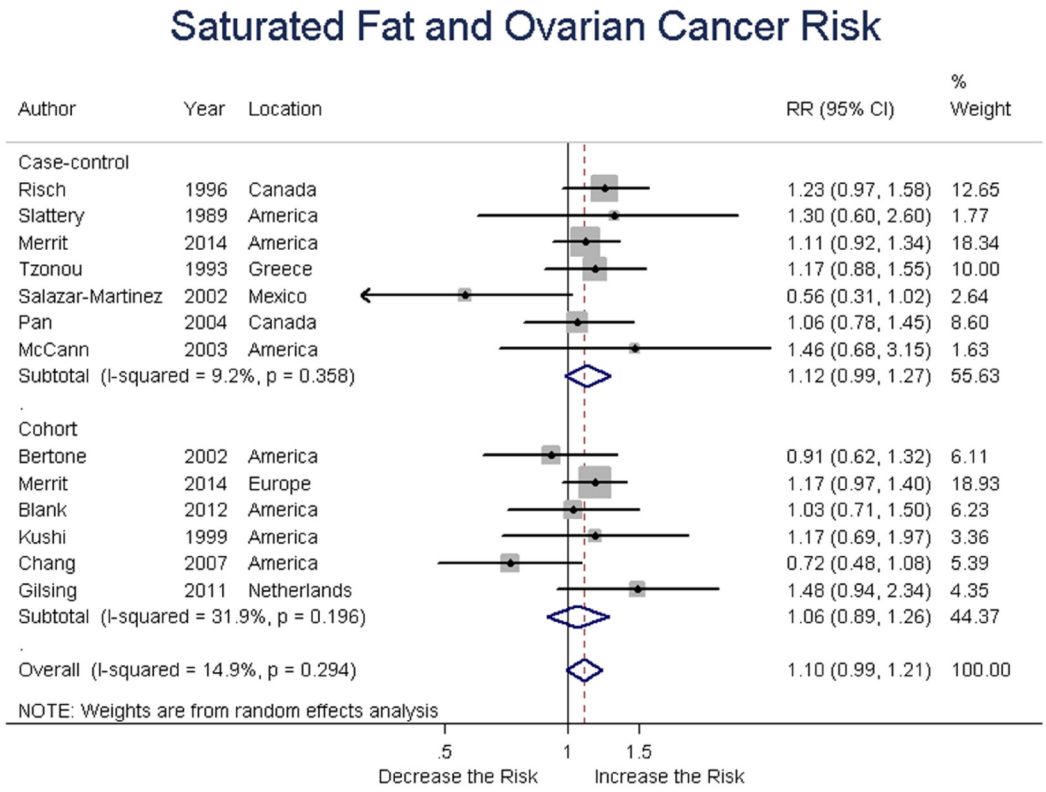

Figure 5: Relationship between saturated fat intake and ovarian cancer risk.

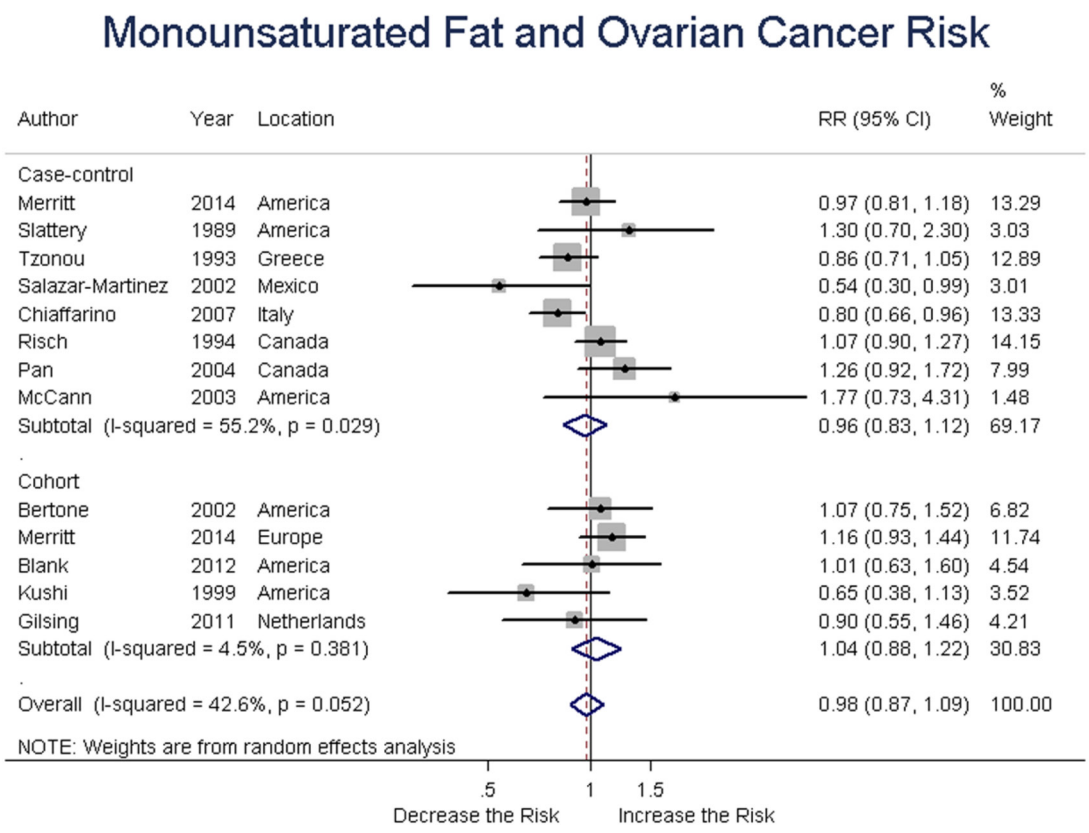

Figure 6: Relationship between monounsaturated fat intake and ovarian cancer risk.

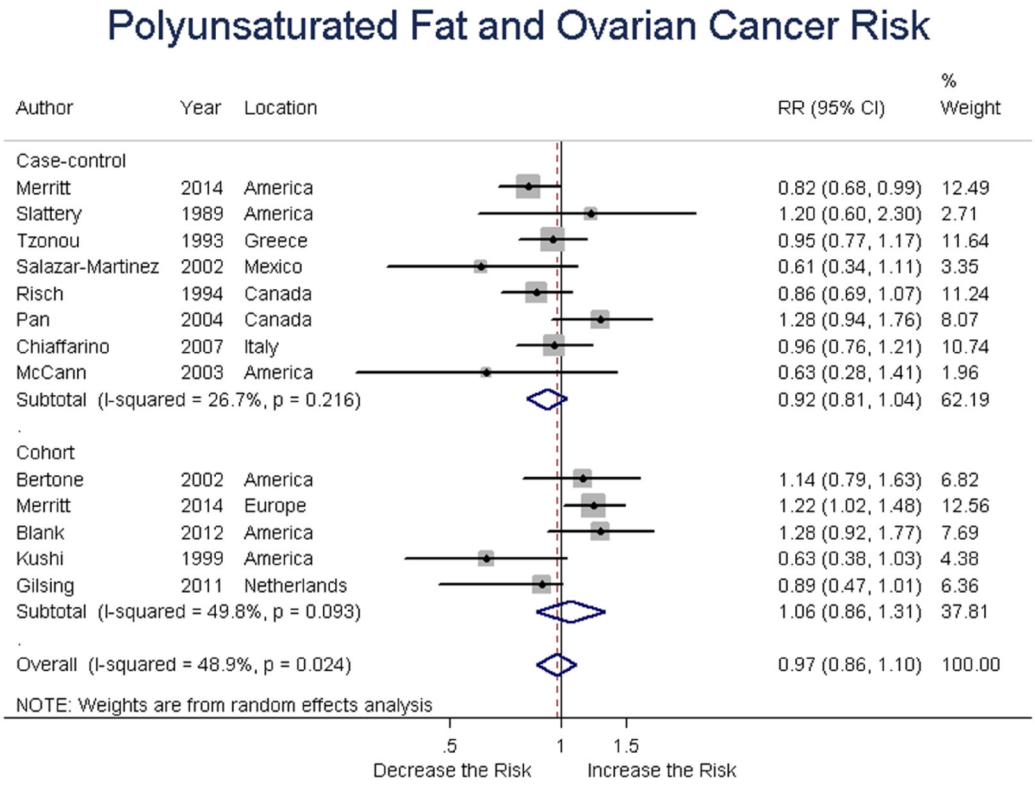

Figure 7: Relationship between polyunsaturated fat intake and ovarian cancer risk.

Table 2: The characteristics and relative risks [RRs; 95% confidence interval (CI)] for cohort studies on dietary fat and ovarian cancer

Author (Country)	Publication yr	Case/Total	Type of Fat	RR (95% CI)	Adjusted confounding factors
Merritt[32] (America)	2014 (1980-2009)	764/95452	Dairy fat	1.01 (0.80-1.27)	Caloric intake, number of pregnancies, parity, OC use , menopausal status, tubal ligation ,family history
Bertone[33] (America)	2002 (1980-1996)	301/80258	Total fat Animal fat Dairy fat Saturated fat Plant fat Monounsaturated fat Polyunsaturated fat Trans fat	1.03 (0.72-1.45) 0.95 (0.66-1.38) 1.06 (0.73-1.54) 0.91 (0.62-1.32) 0.98 (0.68-1.43) 1.07 (0.75-1.52) 1.14 (0.79-1.63) 1.03 (0.72-1.47)	Age, parity, age at menarche, OC use, menopausal status, postmenopausal hormone use, tubal ligation, smoking status
Merritt[34] (Europe)	2014	1095/325007	Total fat Animal fat Plant fat Saturated fat Monounsaturated fat Polyunsaturated fat	1.16 (0.96-1.40) 0.96 (0.80-1.15) 1.22 (0.98-1.52) 1.17 (0.97-1.40) 1.16 (0.93-1.44) 1.22 (1.02-1.48)	OC use, number of children, menopausal status at enrolment, total energy intake
Blank[35] (America)	2012 (1995-2005)	695/151552	Total fat Animal fat Plant fat Saturated fat Monounsaturated fat Polyunsaturated fat	1.28 (1.01-1.63) 1.30 (1.02-1.66) 1.00 (0.79-1.27) 1.03 (0.71-1.50) 1.01 (0.63-1.60) 1.28 (0.92-1.77)	Age, race, education, BMI, family history, OC use, parity, menopausal hormone therapy use, total energy intake
Kiani[36] (America)	2006 (1976-1992)	71/ 13,281	Dairy fat	0.94 (0.70-1.27)	Age, parity and BMI, and also for age at menopause and hormone replacement therapy in postmenopausal analyses
Mommers[37] (Netherlands)	2006 (1986-1997)	252/2216	Dairy fat	1.53 (1.00-2.36)	Age, height, smoking, number of cigarettes smoked daily, OC use and parity, and dairy products
Kushi[38] (America)	1999 (1986-1995)	139/ 29,083	Total fat Animal fat Saturated fat Plant fat Monounsaturated fat Polyunsaturated fat	0.80 (0.47-1.36) 0.98 (0.57-1.69) 1.17 (0.69-1.97) 0.75 (0.44-1.27) 0.65 (0.38-1.13) 0.63 (0.38-1.03)	Age, total energy intake, no. of live births, age at menopause, family history of ovarian cancer, hysterectomy, waist-to-hip ratio, level of physical activity, smoking, education
Chang[39] (America)	2007 (1995-2003)	280/97275	Total fat Saturated fat	0.85 (0.58-1.24) 0.72 (0.48-1.08)	Race, energy intake, parity, OC use, exercise, wine consumption, menopausal status, hormone therapy
Gilsing[40] (Netherlands)	2011 (1986-2002)	340/ 62,573	Total fat Animal fat Plant fat Dairy fat Saturated fat Monounsaturated fat Polyunsaturated fat Trans fat	1.04 (0.73-1.49) 1.30 (0.93-1.83) 0.64 (0.45-0.91) 1.28 (0.91-1.80) 1.48 (0.94-2.34) 0.90 (0.55-1.46) 0.89 (0.47-1.01) 1.51 (1.04-2.20)	Age, total energy intake, parity (number of children), and use of oral contraceptives use

Table 3: Relative risks (RR) of ovarian cancer and corresponding 95% confidence intervals (CI) according to histological types and intake of dietary fat

Types of dietary fat	Histological types							
	Serous tumor		Endometroid tumor		Mucinous tumor		Other tumor	
	RR (95%CI)	*P*	RR (95%CI)	*P*	RR (95%CI)	*P*	RR (95%CI)	*P*
Total fat	1.12(1.01,1.24)	0.025	1.05(0.85,1.30)	0.628	1.15(0.69,1.90)	0.591	1.17(0.69,1.99)	0.561
Animal fat	1.07(1.00,1.16)	0.061	0.96(0.79,1.17)	0.715	1.36(1.08,1.73)	0.011	0.82(0.49,1.38)	0.456
Plant fat	1.07(0.95,1.21)	0.278	0.92(0.76,1.11)	0.391	0.96(0.73,1.27)	0.778	1.22(0.71,2.09)	0.468
Saturated fat	1.26(1.05,1.52)	0.012	1.34(1.08,1.66)	0.008	1.29(0.93,1.81)	0.132	1.19(0.40,3.51)	0.754
Monounsaturated fat	0.97(0.82,1.14)	0.692	0.78(0.57,1.06)	0.115	1.09(0.88,1.35)	0.428	0.84(0.58,1.21)	0.350
Polyunsaturated fat	0.97(0.78,1.21)	0.778	1.07(0.86,1.32)	0.564	1.15(0.93,1.43)	0.203	0.99(0.61,1.62)	0.974
Dairy fat	0.89(0.72,1.10)	0.283	1.13(0.79,1.61)	0.501	1.17(0.62,2.22)	0.631	0.75(0.44,1.27)	0.287
Trans fat	1.26(1.02,1.61)	0.044	1.27(0.89,1.81)	0.466	1.33(0.72,2.44)	0.358	1.10(0.64,1.89)	0.729

P-value for significant test. ($P < 0.050$)
Abbreviations: RR: relative risk, CI: confidence interval

Dietary fat consumption and ovarian cancer subtypes

Five studies involved dietary fat intake and risk of ovarian cancer subtypes. Significant positive association was found between total fat, saturated fat, trans-fat intake and serous ovarian tumor risk. High saturated fat intake was associated with a 34% increase in endometroid ovarian cancer risk. The RR for high animal fat intake was 1.36 (95% CI = 1.08-1.73, $P = 0.011$), suggesting a significant positive association between animal fat consumption and mucinous ovarian cancer risk. (Table 3)

Subgroup and sensitivity analysis

Subgroup analysis stratified by the geographic areas, study types and confounding factors of included studies was performed. Saturated fat (RR = 1.20, 95% CI = 1.04-1.39) and dairy fat (RR = 1.37, 95% CI = 1.05, 1.79) intake could increase ovarian cancer risk in European populations; a positive trend was present among American populations, while an inverse trend was found in other populations (including Asians and South Americans). The conclusions of case-control and cohort studies were basically consistent; however, cohort studies were more inclined to a positive association between dietary fat intake and ovarian cancer risk, though no statistical significance was obtained. The summary results were modified by menopausal status, hormone replacement therapy, BMI, and pregnancy times. (Table 4-1 and Table 4-2.)

Sensitivity analysis showed that the results obtained for the association between saturated fat intake and ovarian cancer risk were significantly influenced by one study [29], which didn't adjust hormone use and pregnancy times.

Publication bias

We found no evidence of publication bias with regard to dietary fat consumption and ovarian cancer risk by means of visual inspection of funnel plots and formal statistical tests, including Begg rank correlation test and Egger linear regression test (all $P > 0.05$).

DISCUSSION

Dietary fat, as one of the most controversial dietary factors in nutritional epidemiology, might elevate the incidence of hormone related cancers, including breast, endometrial and ovarian cancers, but discrepant observational results have been reported. We thoroughly searched the literature, and found the incidence of two important cancer types, breast cancer and stomach cancer, were in relation to the high consumption of dietary fat. Breast cancer was traditionally considered to be linked with western lifestyles, other including prostate and colorectal cancers, and the inflammatory bowel diseases; IBD, Crohn's disease (CD). Stomach cancer was considered to be linked more with eastern lifestyle. The included two meta-analyses [7, 8] indicated positive associations between dietary fat intake and breast and stomach cancer. Considering the regional difference of these two cancers, we can conclude that the effect of dietary fat on cancer risk may be independent of the region. To define the effect of dietary fat on ovarian cancer risk, we conducted this meta-analysis to clear this research subject.

The results of this meta-analysis including case-

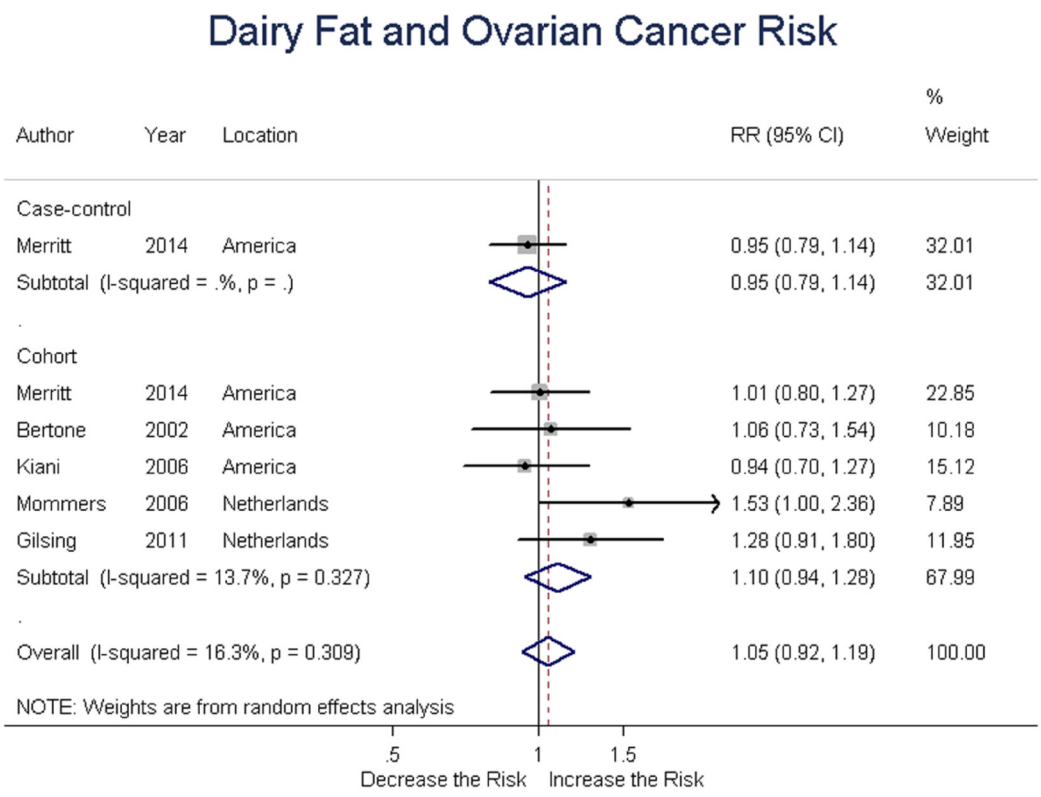

Figure 8: Relationship between dairy fat intake and ovarian cancer risk.

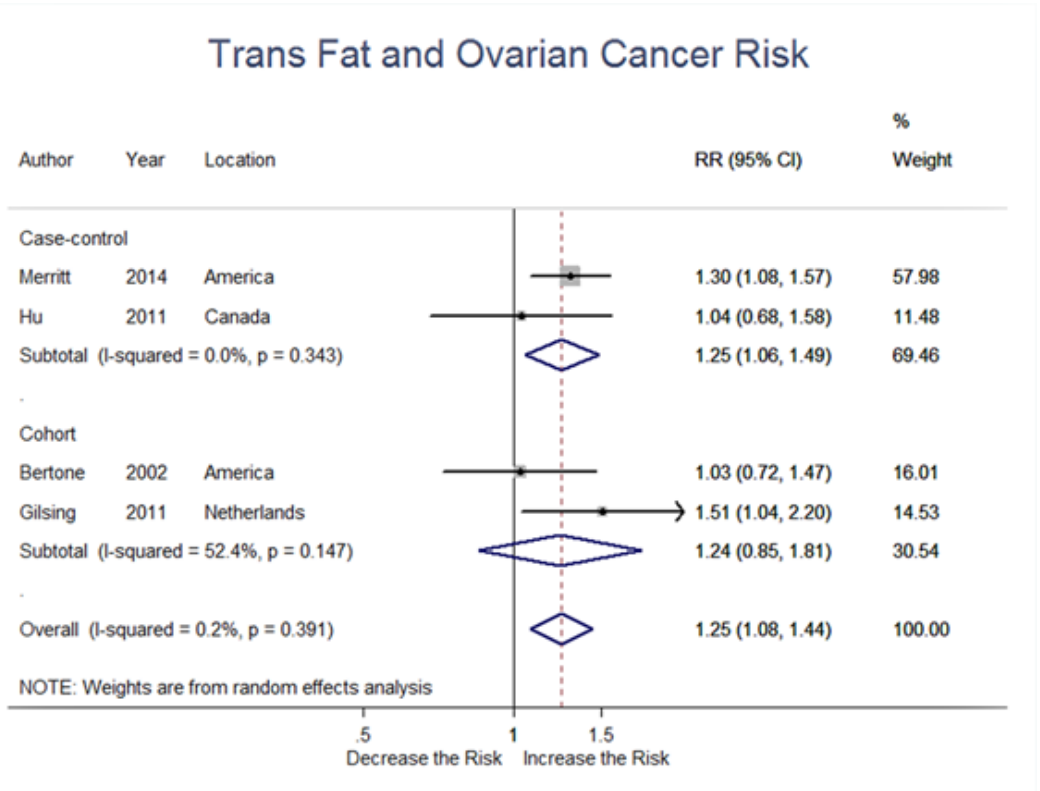

Figure 9: Relationship between trans fat intake and ovarian cancer risk.

Table 4-1: Subgroup analysis based on study characteristics

	Total fat		Animal fat		Plant fat	
	N	RR (95%CI)	*N*	RR (95%CI)	*N*	RR (95%CI)
All studies	17	1.19(1.04,1.37) I^2=60.1%,p=0.001	10	1.21(0.99,1.47) I^2=68.6%,p=0.001	9	0.95(0.83,1.09) I^2=29.2%,p=0.185
Study type						
Case-control	11	1.32(1.06,1.63) I^2=69.8%,p=0.000	5	1.50(0.89,2.53) I^2=82.3%,p=0.000	4	0.96(0.81,1.12) I^2=0.0%,p=0.858
Cohort	6	1.10(0.97,1.24) I^2=4.2%, p=0.389	5	1.09(0.93,1.28) I^2=28.4%,p=0.232	5	0.93(0.74,1.17) I^2=61.7%,p=0.034
Geographic location or country						
America	7	1.08(0.95,1.22) I^2=2.7%, p=0.399	5	1.13(0.96,1.34) I^2=27.9%,p=0.235	4	0,97(0.85,1.11) I^2=0.0%,p=0.805
Europe	4	1.25(0.91.1.73) I^2=83.5%,P=0.000	2	1.08(0.81,1.44) I^2=58.2%,p=0.012	2	0.90(0.48,1.69) I^2=89.2%,p=0.002
Others	6	1.33(0.98,1.82) I^2=63.1%,p=0.019	3	1.69(0.59,4.83) I^2=88.1%,p=0.000	3	0.88(0.62,1.09) I^2=0.0%,p=0.796
Adjusted for						
Total energy						
Yes	12	1.12(0.97,1.29) I^2=48.8%,p=0.034	5	1.07(0.87,1.31) I^2=48.9%,p=0.098	5	0.90(0.70,1.16) I^2=63.2%,p=0.028
No	5	1.39(0.99,1.95) I^2=62.3%,p=0.001	5	1.55(1.00,2.39) I^2=80.1%,p=0.000	4	0.97(0.83,1.13) I^2=0.0%,p=0.936
Family history						
Yes	5	1.16 (0.93,1.44) I^2=44.7%,p=0.143	4	1.17(0.97,1.40) I^2=28.0%,p=0.244	4	0.96(0.84,1.10) I^2=29.2%.p=0.185
No	12	1.20(1.00,1.43) I^2=67.8%,p=0.000	6	1.27(0.89,1.82) I^2=79.3%,p=0.000	5	0.93(0.71,1.22) I^2=59.4%,p=0.043
OC use						
Yes	12	1.28(1.09,1.51) I^2=65.9%,p=0.001	6	1.11(0.97,1.29) I^2=37.1%,p=0.159	6	0.96(0.82,1.14) I^2=49.2%,p=0.080
No	5	0.98(0.79,1.22) I^2=31.5%,p=0.211	4	1.49(0.69,3.21) I^2=84.2%,p=0.000	3	0.85(0.61,1.17) I^2=0.0%,p=0.716
BMI						
Yes	6	1.57(1.24,1.99) I^2=56.3%,p=0.043	3	2.08(1.04,4.14) I^2=81.5%,p=0.004	2	1.00(0.81,1.25) I^2=29.2%,p=0.185
No	11	1.04(0.94,1.16) I^2=17.3%,p=0.284	7	1.03(0.90,1.18) I^2=22.0%,p=0.261	7	0.92(0.77,1.10) I^2=46.5%,p=0.082
Menopausal status						
Yes	9	1.20(0.95,1.51) I^2=75.2%,p=0.000	4	1.29(0.80,2.08) I^2=82.5%,p=0.001	4	1.08(0.90,1.30) I^2=8.4%,p=0.351
No	8	1.17(0.99,1.38) I^2=38.7%,p=0.121	6	1.21(0.98,1.49) I^2=50.0%,p=0.075	5	0.89(0.76,1.05) I^2=25.7%,p=0.185
Hormone use						
Yes	3	1.08(0.85,1.37) I^2=41.7%,p=0.180	2	1.15(0.85,1.55) I^2=48.3%,0.164	2	0.99(0.81,1.21) I^2=0.0%,p=0.982
No	14	1.23(1.04,1.45) I^2=66.6%,p=0.000	8	1.25(0.97,1.62) I^2=73.4%,p=0.000	7	0.92(0.76,1.11) I^2=46.7%,p=0.081
Pregnancy times						
Yes	9	1.10(0.98,1.25) I^2=15.7%,p=0.303	6	1.05(0.8,1.23) I^2=33.5%,p=0.185	6	0.90(0.73,1.11) I^2=0.0%,p=0.990
No	8	1.33(1.01,1.74) I^2=78.2%,p=0.000	4	1.64(1.00,2.69) I^2=80.6%,p=0.001	3	1.00(0.83,1.21) I^2=55.4%,p=0.047

Table 4-2: Subgroup analysis based on study characteristics

	Monounsaturated fat		Polyunsaturated fat		Dairy fat	
	N	RR (95%CI)	*N*	RR (95%CI)	*N*	RR (95%CI)
All studies	13	0.98(0.87,1.09) I^2=42.6%,p=0.052	13	0.97(0.86,1.11) I^2=48.9%,p=0.024	6	1.05(0.92,1.19) I^2=16.3%,p=0.309
Study type						
Case-control	8	0.96(0.83,1.12) I^2=55.2%,p=0.029	8	0.93(0.82,1.05) I^2=26.7%,p=0.216	1	0.95(0.79,1.14)
Cohort	5	1.04(0.88,1.22) I^2=4.5,p=0.381	5	1.06(0.86,1.31) I^2=49.8%,p=0.093	5	1.10(0.94,1.28) I^2=13.7%,p=0.327
Geographic location/country						
America	6	0.98(0.85,1.13) I^2=0.0%,p=0.507	6	0.97(0.76,1.25) I^2=57.9%,p=0.050	4	0.98(0.86,1.10) I^2=0.0%,p0.937
Europe	4	0.92(0.77,1.10) I^2=56.4%,p=0.076	4	1.03(0.89,1.19) I^2=35.3%,p=0.200	2	1.37(1.05,1.79) I^2=0.0%,p=0.524
Others	3	1.00(0.72,1.38) I^2=67.1%,p=0.048	3	0.92(0.65,1.32) I^2=68.8%,p=0.041	0	
Adjust for						
Total energy						
Yes	9	0.98(0.84,1.14) I^2=47.8%,p=0.063	9	099(0.84,1.17) I^2=59.2%,p=0.016	4	1.03(0.87,1.23) I^2=30.4%,p=0.230
No	4	0.93(0.79,1.10) I^2=32.4%,p=0.218	4	0.93(0.80,1.08) I^2=14.6%,p=0.319	2	1.10(0.88,1.37) I^2=21.3%,p=0.260
Family history						
Yes	4	1.00(0.84,1.19) I^2=29.0%,p=0.238	4	0.92(0.73,1.15) I^2=60.8%,p=0.054	2	0.97(0.84,1.12) I^2=0.0%,p=0.684
No	9	0.95(0.82,1.11) I^2=50.6%,p=0.048	9	1.02(0.88,1.18) I^2=42.9%,p=0.092	4	1.15(0.94,1.41) I^2=25.1%,p=0.684
OC use						
Yes	8	0.99(0.89,1.10) I^2=26.4%,p=0.227	8	1.00(0.86,1.15) I^2=55.9%,p=0.034	5	1.08(0.93,1.25) I^2=27.3%,p=0.239
No	5	0.90(0.68,1.20) I^2=61.0%,p=0.036	5	0.93(0.71,1.21) I^2=53.8%,p=0.070	1	0.94(0.70,1.27)
BMI						
Yes	9	1.20(0.94,1.52) I^2=0.0%,p=0.709	9	1.27(1.03,1.58) I^2=0.0%,p=0.984	1	0.94(0.70,1.27)
No	4	0.93(0.83,1.05) I^2=47.0%,p=0.058	4	0.93(0.82,1.05) I^2=49.8%,p=0.043	5	1.08(0.93,1.25) I^2=27.3%,p=0.239
Menopausal status						
Yes	6	1.01(0.83,1.23) I^2=53.9%p=0.070	5	1.10(0.87,1.39) I^2=53.3%,p=0.093	3	1.00(0.85,1.18) I^2=0.0%,p=0.876
No	7	0.93(0.81,1.08) I^2=38.2%,p=0.138	8	0.92(0.82,1.02) I^2=16.6%,p=0.299	3	1.17(0.88,1.57) I^2=62.6%,p=0.069
Hormone use						
Yes	2	1.05(0.79,1.39) I^2=0.0%,p=0.847	2	1.22(0.95,1.55) I^2=0.0%,p=0.642	2	0.98(0.78,1.24) I^2=0.0%,p=0.622
No	11	0.96(0.84,1.09) I^2=52.0%,p=0.027	11	0.95(0.83,1.08) I^2=52.3%,p=0.026	4	1.10(0.91,1.32) I^2=45.5%,p=0.139
Pregnancy times						
Yes	8	1.02(0.89,1.17) I^2=38.6%,p=0.122	8	0.93(0.78,1.12) I^2=62.9%,p=0.009	3	1.02(0.88,1.18) I^2=12.2%,p=0.320
No	5	0.87(0.77,0.98) I^2=0.0%,p=0.047	5	1.02(0.90,1.17) I^2=0.0%,p=0.405	3	1.11(0.85,1.46) I^2=40.6%,p=0.186

P-value for heterogeneity within each subgroup.

control and cohort studies indicated that consumption of total dietary fat and trans fat increased the risk of ovarian cancer. These findings were consistent with the results in specific epidemical studies in NIH-AARP cohort study [35] and an earlier meta-analysis [11], which reported positive associations between total fat intake and EOC risk. Contrasted with our meta-analysis, a pooled analysis [12], three cohort studies [34, 39, 40] and several case-control studies [20, 24, 27, 29] observed no association between total fat consumption and EOC risk. Consistent with a pooled analysis [12] of 12 cohort studies, we observed no significant associations of consumption of dietary fat and risk of ovarian cancer subtypes. There was also no relevance in the associations with dietary fat intake and the risk of different histological subtypes of EOC in an American case-control study [27] and an Italian case-control study [30]. Limited studies involved in associations between dietary fat intakes and EOC risk attribute to different histological subtypes of EOC. Merritt [34] (EPIC) reported high intake of polyunsaturated fatty acids can increase risk for serous EOC. Blank [35] observed an increased risk of serous EOC by total energy from animal fat and inverse associations with risk of EOC observed for the intakes of plant fat and polyunsaturated FAs. Beral [49] reported that serous subtype appeared to have more consistent global distribution, followed by endometrioid subtype, whereas mucinous and clear cell subtypes varied significantly across countries. Among these four main subtypes, the clear cell subtype was least studied, which has higher prevalence in Asia [50-52] and was more frequently found in younger women [52]. In the current meta-analysis, there was only one study [27] from America involving ovarian clear cell carcinoma (OCCC). In addition, the survival outcome of OCCC was comparable to that of serous EOC in terms of early-stage disease [50, 53-55], but worse with respect to advanced-stage disease [56-62]. Therefore, more studies, including epidemiological and clinical studies, should be carried out in Asia and other "new regions" (Central and South America, Africa) [63].

Subgroup analysis based on the characteristics of included studies suggested that menopausal status, hormone replacement therapy, BMI, and pregnancy times can modify the association between dietary fat intake and ovarian cancer risk. These factors are related to exposure to estrogens [64, 65]. A reanalysis [49] of epidemiological data suggested estrogen monotherapy or estrogen and progesterone combination therapy could elevate the risk of ovarian cancer, specifically serous or endometroid tumors. In ovarian tissues, estrogen receptors are also expressed [66]; the ratios of estrogen-DNA adduct depurination to estrogen metabolites and conjugates in ovarian cancer cases are significantly higher than controls [67]. We speculated that hormonal pathways might play a positive role in the development of ovarian cancer. High consumption of dietary fat could stimulate the secretion of extra ovarian estrogen [68, 69], which can exert tumor-promoting activity *via* mitogenic effects on ERα- positive [70, 71] or negative [72] tumor cells, therefore increasing the risk of ovarian cancer [66]. What's more, obese women may suffer from insulin resistance, and concurrent hyperinsulinemia with excess insulin-like growth factor-1 receptor (IGF-1) could additionally induce androgen steroidogenesis [73] and lead to tumor development [74, 75].

An important highlight of our meta-analysis is that we analyzed the association between dietary fat intake and the risk of ovarian cancer subtypes. We found that serous ovarian cancer incidence was more susceptible to dietary fat intake. However, these results should be interpreted with caution. The insufficient number of included cases and potential misclassification of pathological subtypes may contribute to the statistical difference observed.

Several limitations of this meta-analysis should be considered. First, there was substantial heterogeneity across studies assessing the associations of dietary fat intake with ovarian cancer risk. Considering the varieties of the characteristics of included populations, and study designs and types, the existence of substantial heterogeneity was reasonable, and we conducted subgroup analysis to reduce its effect on the results. Second, misclassification bias, which stemmed mainly from the misclassification of dietary assessments and pathological subtypes of ovarian cancer, should be paid enough attention to. Misclassification of dietary assessments may result from the differences across nutrient databases or designed questionnaires. Diagnosis, pathology review, and classification methods could cause misclassification bias of pathological subtypes of ovarian cancer. Third, we couldn't rule out the effects of confounding factors and various statistical biases on our results. Furthermore, controls and confounding factor adjustment methods across individual studies were not consistent. With more and more basic and clinical researches in recent years, and the increasing understanding of the relationship between diet and health, the confounding factors controlled have markedly increased in number, and bias was inevitable. Forth, although no publication bias was found, its possible effect cannot be totally excluded.

In conclusion, the present meta-analysis of case-control and cohort studies indicate that increased consumption of total fat, saturated fat and trans-fat may be associated with an increased risk of ovarian cancer. Among the dietary fats, saturated fats can significantly increase serous and endometroid ovarian cancer, with the risk of serous ovarian cancer more susceptible to dietary fat intake. In addition, subgroup analysis data suggested that menopausal status, hormone replacement therapy, BMI, and pregnancy times may serve as potential effect modifiers. Future studies should focus more on specific pathological subtypes of ovarian cancer as well as the influence of molecular mechanisms and genetic factors on

the association of dietary fat and ovarian cancer.

MATERIALS AND METHODS

Search strategy

We obtained the literature published in any language to December 2015 by fully searching the PubMed database. The search terms used were "diet", "dietary fat" in combination with "ovarian cancer," "ovarian neoplasm" or "ovarian carcinoma", without restrictions. In addition, we reviewed the reference lists of retrieved studies and recent reviews to supplement electronic database searches.

Study selection

Study selection included initial screening of titles or abstracts, and a second one for full texts. Studies were eligible for inclusion if they met the following criteria: 1) observational studies which enrolled patients with proven epithelial ovarian cancers excluding tumors of "borderline malignant potential " histopathology, 2) patients enrolled were adults (≥18 yr of age), 3) studies containing available data showing association(s) between intake of dietary fat (total, saturated, animal, dairy or unsaturated fat) and ovarian cancer, and 4) odds ratio or relative risk (RR) with 95% confidence interval (CI) for each variable or availability of raw data to calculate these parameters.

Data extraction

All data were extracted with a data-collection form. Information was recorded as follows: last name of the first author, publication year, study population, period, country, sample size; risk estimate from multivariable model for the highest *versus* lowest category of dietary fat intake with the corresponding 95% CI; statistical adjustment for the main confounding factors of interest.

Data extraction and study selection were performed by 3 authors (Qiu WL, Lu H and Qi YN) independently. Any disagreements were resolved by discussion.

Statistical methods

The association between dietary fat consumption and the risk of ovarian cancer was our main analytical object. Dietary fats in this meta-analysis were defined as total fat, animal fat, plant fat, dairy fat, saturated fat, monounsaturated fat, polyunsaturated fat and trans-fat. Relative risk (RR) was used as the common measure of association in this meta-analysis, and the random-effects model was selected to calculate summary RRs and 95% CIs associated with dietary fats. Q statistic (significance level at $P < 0.10$) and I^2 statistic, a quantitative measure of inconsistency across studies [13], were applied for heterogeneity assessment of RRs across studies. Subgroup analyses stratified by geographic region (country), study type, and study characteristics were carried out to investigate potential sources of heterogeneity. Sensitivity analyses were performed by excluding one study at a time to assess the influence of a single study on the overall risk estimate. Publication bias was assessed with funnel plots, Egger's test [14], and Begg's test [15] (all $P > 0.05$). The Stata version 12.0 software (StataCorp) was used for statistical analyses.

Abbreviations

EOC: epithelial ovarian cancer; RR, relative risk; OR, odds ratio; CI, confidential interval; BMI: body mass index.

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Xiuwen Wang and Wenlong Qiu participated in the design of this article. Wenlong Qiu, Heng Lu and Yana Qi participated in abstracting the data and Wenlong Qiu performed statistical analysis. Xiuwen Wang and Wenlong Qiu wrote the paper. All authors read and approved the final article.

CONFLICTS OF INTEREST

There is no conflict of interest of this study.

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